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Gastrointestinal symptoms in COVID-19 patients

Gastrointestinalni simptomi bolesnika sa COVID-19

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Abstract

Background/Aim. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global threat and a huge problem for our community. There are so many open questions. The aim of this study was to establish the frequency of gastrointestinal (GI) symptoms in hospitalized patients with infection caused by this virus (coronavirus disease-19 – COVID-19), but also to compare if patients with GI symptoms have a higher computed tomography (CT) scan severity score of interstitial pneumonia (IP) compared to patients with COVID-19 without GI symptoms. **Methods**. Our database comprised 322 patients with COVID-19 who were divided into two groups, patients with and without GI symptoms. All information was taken from anamnestic data and patients' history, followed by statistical analysis. **Results.** Thorax CT scans of 206 patients (63.9%) were described as bilateral IP, of which 76 CT scans (36.9%) were described by radiologists as the peak of infection. Moreover, 130 patients (40.4%) had GI symptoms, and even 58 out of 130 patients (44.6%) reported GI symptoms as the first manifestation of COVID-19 infection. The most commonly reported one was the lack of appetite (73 patients or 56.15%). Furthermore, 65 (50%) patients reported diarrhea, 25 (19.2%) patients reported nausea and vomiting, and 9 (6.9%) patients reported abdominal pain. In addition, among patients with bilateral IP and GI tract symptoms, 31 (40.79%) of them did not have a higher CT scan severity score at the peak of the disease compared to the patients without GI symptoms (45 of them or 59.2%), (p = 0.704). **Conclusion.** GI symptoms often are the first manifestation of COVID-19. Therefore, every patient with newly formed digestive tract symptoms should be tested for COVID-19. On the other hand, GI symptoms do not indicate COVID-19 patients will have a severe form of IP.

Key words:
covid-19; diagnosis; diarrhea; feeding and eating disorders; sars-cov-2; severity of illness index; signs and symptoms, digestive; tomography, x-ray computed.

Apstrakt

Uvod/Cilj. Teški akutni respiratorni sindrom korona virus 2 (SARS-CoV-2) je globalni problem i pretnja, i još uvek ima puno otvorenih pitanja. Cilj ispitivanja bio je da se utvrdi učestalost gastrointestinalnih (GI) simptoma kod hospitalizovanih bolesnika sa infekcijom prouzrokovanom SARS-CoV-2 (*coronavirus disease*-19 – COVID-19), kao i da se utvrdi da li ti bolesnici imaju viši skor intersticijalne pneumonije (IP) na pregledu pluća kompjuterizovanom tomografijom (KT) u odnosu na bolesnike sa COVID-19 bez GI tegoba. **Metode.** Ispitivanje je obuhvatilo 322 hospitalizovana bolesnika sa COVID-19 koji su bili podeljeni u dve grupe: grupu sa GI simptomima i grupu bez GI simptoma. Svi podaci su dobijeni anamnestički i iz istorije bolesti bolesnika, a nakon toga su statistički obrađeni. **Rezultati**. Od 322 bolesnika, 206 (63.9%) je imalo opisanu obostranu IP na KT pregledu grudnog koša, a 76 bolesnika (36.9%) imalo je opisanu IP u vrhuncu bolesti. Takođe, 130 bolesnika (40.4%) prijavilo je GI simptome, čak 58 od 130 bolesnika (44.6%) je anamnestički navelo da su GI simptomi bili prva manifestacija COVID-19 infekcije. Najčešći simptom bio je gubitak apetita [kod 73 bolesnika (56.15%)]. Od 130 bolesnika sa GI simptomima, 65 (50%) je prijavilo dijareju, 25 (19.23%) mučninu i povraćanje, a 9 (6.9%) bolesnika prijavilo je bol u trbuhu. Bolesnici sa obostranom IP i GI simptomima [31 (40.8%)] na vrhuncu bolesti nisu imali veću zahvaćenost plućnog parenhima IP na pregledu grudnog koša KT, u poređenju sa bolesnicima bez GI simptoma [45 (59.21%)], (p = 0.704). **Zaključak**. GI simptomi su često prva manifestacija COVID-19. Stoga,

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kod svih bolesnika sa novonastalim digestivnim simptomima treba proveriti postojanje COVID-19. S druge strane, prisustvo GI simptoma ne ukazuje na to da će bolesnici sa COVID-19 imati teži oblik IP.

Ključne reči:
covid-19; dijagnoza; dijareja; ishrana, poremećaji; sars-cov-2; bolest, indeks težine; znaci i simptomi, digestivni; tomografija, kompjuterizovana, rendgenska.

Introduction

As it is known, the first human cases of coronavirus disease-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were observed in December 2019 in Wuhan, a city in China [1]. The causative agent of those types of pneumonia was investigated, and it was discovered that there was a new type of human-infecting Betacoronavirus named SARS-CoV-2 [2]. The Chinese government declared that the outbreak of the SARS-CoV-2 virus first started in the Huanan seafood market in Wuhan [3]. After only one month, the World Health Organization (WHO) announced that SARS-CoV-2 became a Public Health Emergency of International Concern [4]. Now, it is obvious that this outbreak caused the 21st-century pandemic [5]. As COVID-19 typically causes viral pneumonia, it is easy to conclude that the route of transmission is mainly through contact with respiratory droplets. The most commonly reported symptoms of COVID-19 were fever, cough, and fatigue, as this virus predominantly attacks the respiratory tract of the human host [6]. Other less common but equally clinically important symptoms include gastrointestinal (GI) tract symptoms such as diarrhea, abdominal pain, vomiting, and loss of appetite [6]. In radiology, the computed tomography (CT) scan stage of interstitial pneumonia (IP), described as the peak of infection, is defined by "consolidation, which refers to an area of homogeneous increase in lung parenchymal attenuation that obscures the margins of vessels and airway walls" [7].

We conducted a retrospective cohort analysis of GI symptoms seen in COVID-19 patients and compared whether those symptoms correlate with the severity of the disease.

Methods

This study was carried out at the University Hospital Medical Center "Bežanijska Kosa", in Belgrade, Serbia, including 324 patients hospitalized either with IP or with positive reverse transcription-polymerase chain reaction (RT-PCR) test on SARS-CoV-2, in the COVID-19 unit, from June 2020 to August 2020. Two patients were excluded because of missing data, making the total number of patients in our database 322. The database contains patients' age, dates of admission to the hospital, dates of hospital discharge, RT-PCR test results of SARS-CoV-2 and SARS-CoV-2 serology testing, oxygen support, CT scan severity scores (0 to 25), CT scan stage of the disease, and GI symptoms. Data on comorbidities were also added [arterial hypertension (AH), diabetes mellitus (DM) type 2, asthma and chronic obstructive pulmonary disease, and history of malignant diseases]. Weight and height were obtained from 101 patients for calculating and calculated to body mass index (BMI). The presence of GI symptoms was obtained on admission, and it included diarrhea, nausea/vomiting, abdominal pain, and lack of appetite. All the information was taken from the patient's history (electronic medical records) and anamnestic data, from admission through discharge.

Statistical analysis was performed using Python 3.7, and descriptive statistics were used to analyze the data. Categorical variables were expressed as counts with proportions. Patients were divided into groups depending on the presentation of GI symptoms and their respective peak CT scan severity scores, including also their age and BMI, which were compared using the *t*-test, while the χ^2 test was used for correlation between gender and the presence of GI symptoms (the level of significance was $p = 0.05$). Further, the Spearman's correlation was used to compare patients' BMI and their respective CT scan severity score of IP at the peak of the disease (the level of significance was $p = 0.05$).

Ethical approval for the study was obtained from the Ethics Committee of the University Hospital Medical Center "Bežanijska Kosa" (approval number 5197/2, from 19.08.2020).

Results

The study included 322 patients; the youngest was 21 years old, while the oldest was 86 (Figure 1). The average patient age was 57. Total hospital stay length ranged from 2 to 56 days, with an average length of stay of approximately 12 days. The BMI of 101 patients was in the range between

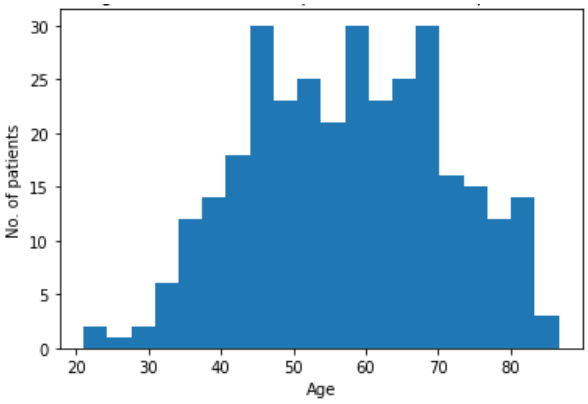


Fig. 1 – Age (years) distribution of coronavirus disease-19 (COVID-19) patients included in this study.

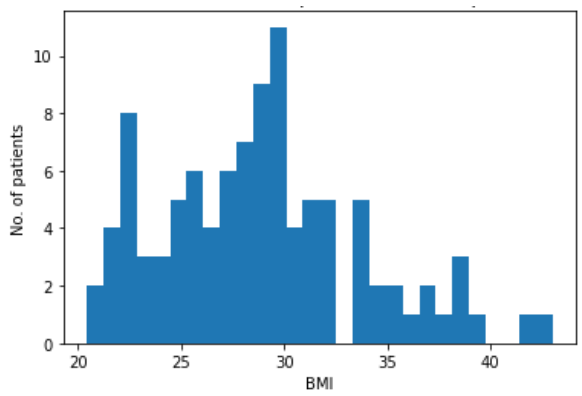


Fig. 2 – Body mass index [BMI (kg/m^2)] distribution of coronavirus disease-19 (COVID-19) patients included in this study.

20 kg/m^2 and 42 kg/m^2, with the average value being 28 kg/m^2 (Figure 2). RT-PCR SARS-CoV-2 test was done in 318 out of 322 patients (98.75%); 214 patients had a positive test result (67.3%). During the hospital stay, additional serological testing was performed: 67 patients (20.8%) were tested for IgM and IgG SARS-CoV-2 antibodies, 19 (28.35%) of them had both IgM and IgG antibodies, 1 of them had only IgM antibodies, 16 (23.9%) of them had IgG antibodies, and 31 (46.3%) had no antibodies. Furthermore, 15 out of 322 patients (4.65%) tested negative with RT-PCR SARS CoV-2 but had positive serology. Chest CT scans of 206 patients (63.9%) were described as bilateral IP (Figure 3), out of which 76 CT scans (36.9%) were described by radiologists as the peak of infection. The oxygen supply was required in 240 patients (74.5%). As mentioned above, data on comorbidities were also included in this database. In addition, 156 patients (48.4%) had AH, 22 patients (6.8%) had asthma or chronic obstructive pulmonary disease, 16 (4.9%) had DM type 2, and 48 patients (14.9%) had a history of malignant diseases. Moreover, 130 patients (40.4%) had GI symptoms, and even 58 out of 130 patients (44.6%) reported GI symptoms as the first manifestation of COVID-19. The most commonly reported one was the lack of appetite (73 patients or 56.15%). Furthermore, 65 out of 130 patients (50%) reported diarrhea, 25 out of 130 patients (19.2%) reported nausea and vomiting, and 9 out of 130 patients (6.9%) reported abdominal pain. Additionally, lack of appetite was reported in 73 of our patients (22.7%), while out of 322 patients, 65 (20.2%) reported diarrhea, 25 (7.8%) reported nausea and vomiting, and 9 (2.8%) reported abdominal pain. In addition, we tested the correlation between age, gender, and BMI and the presence of GI tract symptoms and concluded there was no correlation (p = 0.947, p = 0.187, and p = 0.321, respectively). We also tested the correlation of CT scan severity score of bilateral IP at the peak of infection in patients with (31 of them or 40.8%) and without (45 of them or 59.2%) GI tract symptoms (Figure 4). We concluded that there is no statistically significant difference between those two groups. Namely, patients with bilateral IP and GI tract symptoms did not have a higher CT scan severity score at the peak of the disease compared to the patients without GI symptoms (p = 0.704). In addition, the correlation between CT scan severity score of bilateral IP at the peak of infection and BMI was tested, but there was no correlation (p = 0.796).



Fig. 3 – Computed tomography (CT) scan of bilateral interstitial pneumonia (CT scan severity score 25).

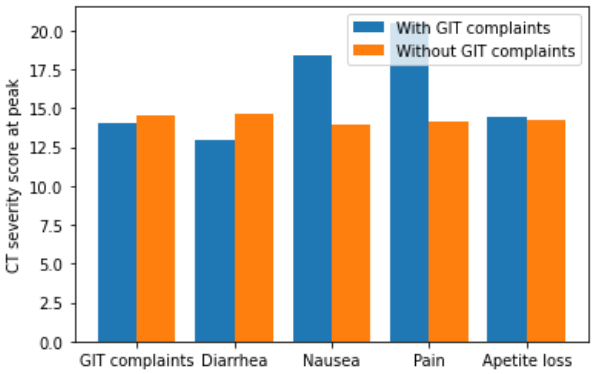


Fig. 4 – Interstitial pneumonia computed tomography (CT) scan severity scores at peak of the disease in coronavirus disease-19 (COVID-19) patients with and without gastrointestinal tract (GIT) symptoms.

Discussion

The age of patients with COVID-19 infection in our study was between 21 and 86 compared to studies in which the median age of patients was between 34 and 59 [8, 9]. The result we obtained had a strong background. Advanced age has been clearly identified as a major risk factor for the development of severe COVID-19 that requires hospital treatment [10]. On the other hand, there was no correlation between a patient's age or gender and the presence of GI symptoms in our study (p = 0.947, p = 0.187, respectively).

Furthermore, this viral infection will more likely infect patients with comorbidities, especially cardiovascular diseases (CD) and DM [11]. It is obvious that there is, as well, a correlation between obesity and COVID-19 disease severity and mortality. As already mentioned, patients with certain comorbidities will have a more severe clinical

manifestation of this viral infection, and obese patients are more prone to CD and DM type 2. In obese patients, excessive adipose tissue stimulates adipocytes to release pro-inflammatory mediators predisposing the body to a pro-inflammatory state and oxidative stress [12]. One more reason for obese patients to have the severe form of COVID-19 is that angiotensin-converting enzyme 2 (ACE2) is expressed in adipocytes [13]. It has been shown that the receptor for ACE2 is crucial for the virus to enter a cell [14]. In our study, there was no correlation between BMI and the presence of GI tract symptoms (p = 0.321), even though BMI ranged from 20 kg/m^2 to 42 kg/m^2, with an average BMI of 28 kg/m^2, and it is found in the literature that BMI equal or higher than 25 kg/m^2 [15] is considered overweight. In comparison to one study in the United States of America (USA), the most common comorbidities were AH, obesity, and DM [16]. In our study, AH is the leader of comorbidities as 48.4% of our patients had it, and there were only 4.9% of patients with DM type 2.

Compared to a study that concluded that approximately 75% of patients had bilateral pneumonia, our result of 63.9% of patients with bilateral IP was almost equal [11]. Moreover, radiology findings depended on the patients' age, disease progression, immunity status, patients' comorbidities, and initial management of disease presentation [17]. In some radiology studies, pneumonia seen on CT scans of patients with COVID-19 infection was described as unusual. All of them showed multifocal patchy "ground-glass" opacities on the periphery of the lungs [18]. In other words, a typical CT scan finding is bilateral IP with "ground glass" opacities and consolidation [8, 19]. By reviewing the literature, we confirmed exactly what we had concluded during our COVID-19 clinical practice. After 0 to 2 days of onset of the disease symptoms, 56% of patients had a normal CT scan finding [20]; afterward, the lesions on the CT scan gradually progressed as an extension of the density of lung opacities [21]. However, chest CT scans are very important in diagnosing COVID-19 as a patient can have a nasopharyngeal swab test for SARS-CoV-2 negative by PCR test, but CT scanning could detect bilateral COVID-19 IP even if the patient did not have clinical symptoms [22].

One study reviewed 15 articles on GI symptoms in COVID-19. The study concluded that the frequency of GI symptoms varied from 3% to 39.6% [14]. Like every other virus infections, this one can also have different clinical manifestations. First of all, we need to emphasize that a significant number of patients in our study had GI symptoms as the first manifestation of COVID-19 (44.6%), so every physician must suspect COVID-19 when a patient at risk presents with only GI symptoms. In all reviewed articles, the predominantly reported symptom was diarrhea [14], opposite to our result that showed lack of appetite as the most frequent one. On the other hand, two doctors from Wuhan got the same result as in this study, with 81 out of 103 patients (79%) with a lack of appetite, following diarrhea, vomiting, and abdominal pain, respectively [23]. Furthermore, there is a report of COVID-19 hospitalized patients in Wuhan, with 3% of them having diarrhea and all of them with a mild clinical picture. In other words, none of the patients needed intensive care [8]. Another report indicated a higher prevalence of diarrhea in patients hospitalized in intensive care units [24]. In the same study, nausea was reported in 10%, vomiting in 4%, and abdominal pain in 2% of the patients [24]. They also reported that patients hospitalized in intensive care units are more likely to have abdominal pain than patients hospitalized in non-intensive care units [24]. This also cannot be correlated because all of our patients were hospitalized in a non-intensive care unit. Although in our study, out of all GI symptoms, the most prevalent was the lack of appetite, diarrhea was also not negligible because 50% of patients reported it. This is a similar result as in one report from the USA, specifically New York, stating that mild diarrhea could reach a prevalence of more than 50% of patients admitted with COVID-19 [5].

We come to a question – how does SARS-CoV-2 infect the GI tract, causing mainly diarrhea? Angiotensin-converting enzyme 2 (ACE2) receptor is crucial for the virus to enter a cell [14]. These receptors are identified in alveolar cells type 2 in the lungs but also in the glandular cells of the stomach and epithelial cells (enterocytes) in the ileum and colon [14, 25, 26]. When SARS-CoV-2 enters the GI tract, specifically enterocytes, it leads to malabsorption, unbalanced intestinal secretion, and activated enteric nervous system, which results in diarrhea [25]. It must be mentioned that the same mechanism for entering GI cells was seen in the previous SARS-CoV epidemic, more precisely via the ACE2 receptor [27].

Furthermore, there is a study about the correlation between GI tract symptoms and severity of the disease, and it shows that almost 23% of patients with GI tract symptoms had a severe clinical picture, and there was also a statistically significant number of patients with GI tract symptoms that needed mechanical ventilation [28]. Nevertheless, there was no difference in inflammatory markers in COVID-19 patients with and without GI tract symptoms [28].

Despite all of these presented facts, we did not found any correlation between radiological findings and GI symptoms, nor between radiological findings and BMI. As we already mentioned, a chest CT scan was done on 206 patients, and radiologists described them with CT scan severity score and stage. CT scan severity score range was 0 to 25, and stages were initial, progressive, peak, late, and resolution. Most of our patients, more precisely 76 of them, were at the peak of bilateral IP with a wide range of CT scan severity scores during hospitalization. Thus, we tested the correlation of CT scan severity score of bilateral IP at the peak in patients with and without GI tract symptoms. We concluded that there was no statistically significant difference between those two groups of patients. In other words, patients with bilateral IP and GI tract symptoms did not have a higher CT scan severity score at the peak of the disease compared to the patients without GI symptoms (p = 0.704). The average CT scan severity score at the peak of the disease in patients with GI symptoms was 14, and in patients without GI symptoms was 14.53. Although we found no difference between radiological findings and GI symptoms,

there is a study about the correlation in patients with and without diarrhea. They also did not find any difference in the laboratory and radiological findings, but they indicated COVID-19 patients with diarrhea had headaches, fatigue, cough, nausea, and vomiting more frequently than patients without diarrhea [29]. On the other hand, it was expected that the obese patients would have a more severe CT scan score of bilateral IP at the peak of the disease, but the results were different. We found no correlation between BMI and radiological findings on a CT scan of the thorax at the peak of the disease ($p = 0.796$).

In all reviewed literature, as well as in this study, all data about GI symptoms are taken from anamnestic data from patients that were hospitalized. Because of that, there is a gap because patients with a mild clinical picture that were not hospitalized were not included and could influence the results [30]. Furthermore, one study concluded that patients without GI symptoms were with a milder clinical picture, and they spent fewer days in hospital than those with GI symptoms. They believe this is due to viral replication in the GI tract causing a more severe clinical picture or because patients with GI symptoms get respiratory symptoms later on and are admitted to a hospital afterward [31]. Discussing viral replication in the GI tract, it is important to emphasize the potential route of transmission through the GI tract (the fecal-oral route). Therewith, stool samples are not normally used for the diagnosis of COVID-19. The priority is still the nasopharyngeal swab which undergoes RT-PCR. It is now known that SARS-CoV-2 RNA is present in patients' stool [5]. Moreover, it is reported that stool samples remained positive for SARS-CoV-2 RNA longer compared to nasopharyngeal swabs [32]. Furthermore, one report showed a COVID-19 patient with more than one nasopharyngeal swab tested negative for SARS-CoV-2 but still positive for SARS-CoV-2 in stool [33]. Compared to previous SARS studies, when the SARS-CoV epidemic started, 16–73% of patients had diarrhea, usually within the first week after the infection [34]. SARS-CoV could also be found in the stool, but active viral replications were shown in histopathological biopsy findings of both small and large intestines as well [35]. Knowing these facts, there is, obviously, a way for fecal-oral transmission of this virus, but also, this mode of transmission may occur after viral clearance from the respiratory tract [22]. If this is true, then the nasopharyngeal swab should be replaced with a rectal swab for testing on SARS-CoV-2 before hospital discharge [36, 37].

The autopsies are crucial for confirming the relationship between COVID-19 and GI tract. There is an autopsy report about an elderly man with COVID-19 infection, and the autopsy revealed segmental dilatation and stenosis in the small intestine, but there is no proof that these are mainly due to COVID-19 infection [25].

Conclusion

Digestive symptoms are often seen as the first manifestation of SARS-CoV-2 infection. Therefore, every patient with newly formed GI tract symptoms, especially the immunocompromised patients, should be tested for COVID-19 in the context of the ongoing global pandemic. As it is known, COVID-19 is a systemic disease, and GI symptoms seen in this infection ratify this fact. On the other hand, GI symptoms do not indicate the patient will have a severe form of IP.

Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Wang C, Horby PW, Hayden FG, Gao GF.* A novel coronavirus outbreak of global health concern. Lancet 2020; 395(10223): 470–3.
2. *Lu R, Zhao X, Li J, Niu P, Yang B, Wu H,* et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395(10224): 565–74.
3. *Shahid Z, Kalayanamitra R, McClafferty B, Kepko D, Ramgobin D, Patel R,* et al. COVID-19 and Older Adults: What We Know. J Am Geriatr Soc 2020; 68(5): 926–9.
4. *Burki TK.* Coronavirus in China. Lancet Respir 2020; 8(3): 238.
5. *Hajifathalian K, Mahadev S, Schwartz RE, Shah S, Sampath K, Schnoll-Sussman F,* et al. SARS-COV-2 infection (coronavirus disease 2019) for the gastrointestinal consultant. World J Gastroenterol 2020; 26(14): 1546–53.
6. *Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz E,* et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. J Clin Med 2020; 9(6): 1753.
7. *Lee KS, Han J, Chung MP, Jeong YJ.* Consolidation. Radiol Illust Chest Radiol 2013; 221–33.
8. *Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y,* et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497–506.
9. *Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L,* et al. Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA 2020; 323(14): 1406–7.
10. *Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z,* et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229): 1054–62.
11. *Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y,* et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507–13.
12. *Ellulu MS, Patimah I, Khaza H, Rahmat A, Abed Y.* Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci 2017; 13(4): 851–63.
13. *Albini A, Di Guardo G, Noonan DMC, Lombardo M.* The SARS-CoV-2 receptor, ACE-2, is expressed on many different cell types: implications for ACE-inhibitor- and angiotensin II receptor blocker-based cardiovascular therapies. Intern Emerg Med 2020; 15(5): 759–66.
14. *Schmulson M, Dávalos MF, Berumen J.* Beware: Gastrointestinal symptoms can be a manifestation of COVID-19 (Spanish). Rev Gastroenterol Mex 2020; 85(3): 282–7.
15. *Chooi YC, Ding C, Magkos F.* The epidemiology of obesity. Metabolism 2019; 92: 6–10.

16. *Richardson S, Hirsch JS, Narasimhan M, Crawford JM, Mcginn T, Davidson KW*. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area. JAMA 2020; 323(20): 2052–9.
17. *Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP,* et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020; 7(1): 4.
18. *Chan JF, Yuan S, Kok K, To KK, Chu H, Yang J*, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395(10223): 514–23.
19. *Lei J, Li J, Li X, Qi X*. CT Imaging of the 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology 2020; 295(1): 18.
20. *Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N,* et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology 2020; 295(3): 200463.
21. *Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X*, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). Radiology 2020; 295(1): 202–7.
22. *Neurath MF*. Covid-19 and immunomodulation in IBD. Gut 2020; 69(7): 1335–42.
23. *Yang L, Tu L*. Implications of gastrointestinal manifestations of COVID-19. Lancet Gastroenterol Hepatol 2020; 5(7): 629–30.
24. *Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J*, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020; 323(11): 1061–9.
25. *Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z,* et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. Gut 2020; 69: 1010–8.
26. *Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H*. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020; 158(6): 1831–1833.e3.
27. *Wan Y, Shang J, Graham R, Baric RS, Li F*. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol 2020; 94(7): e00127–20.
28. *Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM*, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020; 69(6): 1002–9.
29. *Wei XS, Wang X, Niu YR, Ye LL, Peng WB, Wang ZH,* et al. Diarrhea is associated with prolonged symptoms and viral carriage in COVID-19. Clin Gastroenterol Hepatol. (2020) 18:1753–9.e2.
30. *Wei XS, Wang X, Niu YR, Ye LL, Peng WB, Wang ZH,* et al. Clinical Characteristics of SARS-CoV-2 Infected Pneumonia with Diarrhea. 2020. Available from: https://papers.ssrn.com › papers
31. *Guan W, Ni Z, Hu Y, Liang W, Ou C, He J,* et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382(18): 1708–20.
32. *Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J,* et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020; 115(5): 766–73.
33. *Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X*, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol 2020; 5(5): 434–5.
34. *Chen L, Lou J, Bai Y, Wang M*. COVID-19 Disease with Positive Fecal and Negative Pharyngeal and Sputum Viral Tests. Am J Gastroenterol 2020; 115(5): 790.
35. WHO issues consensus document on the epidemiology of SARS. Wkly Epidemiol Rec 2003; 78(43): 373–5. (English, French)
36. *Wong SH, Lui RN, Sung JJ*. Covid-19 and the digestive system. J Gastroenterol Hepatol 2020; 35(5): 744–8.
37. *Yeo C, Kaushal S, Yeo D*. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Lancet Gastroenterol Hepatol 2020; 5(4): 335–7.

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